REMARKS

I. Status of the claims

Claims 9-20 are pending. Claims 9-20 stand rejected under 35 U.S.C. §§ 112, second paragraph, 102(b/e) and 103(a).

II. Rejection of claims 9-20 under 35 U.S.C. § 112, second paragraph

Reconsideration is requested of the rejection of claims 9-20 under § 112, second paragraph as being indefinite.

The Office asserts that claims 9-20 are ambiguous regarding whether a composition, compound or pharmaceutical composition is being claimed. In response, claims 9-20 have been amended by replacing "combination" with "composition."

Claims 10-19 are further rejected under § 112, second paragraph, as being ambiguous due to having trademarks in the claims. The specification has been amended to include the chemical name of trademarks or trade names appearing in the claims.[1] Moreover, claims 10-19 have been amended so that each trademark or trade name has been replaced with its chemical name.

In light of these amendments, claims 9-20 satisfy the requirements of § 112, second paragraph.

III. Rejection of claims 9-20 under 35 U.S.C. § 102(b) or (e)

Reconsideration is requested of the rejection of claims 9-20 under § 102(b) or (e) as anticipated by Isakson et al.[2] ("Isakson I"); Gregory et al.[3]; Isakson et al.[4] ("Isakson II"); and Engelhardt[5].

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[1]No new matter is added by this amendment; the trademarked names and trade named compounds used in the specification and claims are merely identified by their chemical name in the amendment. In support of this amendment, Applicants enclose copies of abstracts in which certain of the compounds are named by their chemical name, and CAS registration information in which the chemical name is given for the remainder of the compounds.

[2]U.S. Patent No. 6,136,839.

[3]U.S. Patent No. 6,407,140.

[4]PCT Document No. WO 96/41626.

[5]Chem. Abst. 125:292089.

Claim 9, as amended, is directed toward a composition comprising a **cyclooxygenase-2 inhibitor** (COX-2), a **5-lipoxygenase inhibitor** (5-LO) and an **immunosuppressive drug** selected from antiproliferative agents, antiinflammatroy-acting compounds and inhibitors of leukocyte activation.

Isakson I and Isakson II describe combinations and compositions comprising a COX-2 inhibitor and a 5-LO inhibitor. As noted by the Office, both mention that the pharmaceutical compositions may further comprise a pharmaeutically-acceptable carrier, diluent and/or adjuvant, "and, if desired, other active ingredients."[6] But nowhere do Isakson I or Isakson II disclose or suggest that the "other active ingredient" should be an **immunosuppressive drug**, as required by claim 9.

The Office further asserts in support of its rejection that Gregory et al. disclose combinations of "COX-2 inhibitors, 5-lipoxygenase inhibitors and other active ingredients."[7] This is not correct. Rather, they disclose combinations comprising a COX-2 inhibitor, **a leukotriene A_4 hydrolase** (LTA4) inhibitor, and an immunosuppressive agent. Claim 9 requires a 5-L0 inhibitor not a LTA4 inhibitor. 5-LO inhibitors are not the same as LTA4 inhibitors.[8]

Moreover, the Office also asserts that Engelhardt disclose "a combination therapy of several active ingredients including COX-2 inhibitors, leukocyte inhibitors and 5-LO inhibitors."[9] This is not correct. The Engelhardt reference is an abstract of an article[10] that describes findings of a new non-steroidal anti-inflammatory drug (NSAID), meloxicam. The abstract does disclose that meloxicam preferentially inhibits COX-2 leukocyte migration. But nowhere do Engelhardt disclose the combination of COX-2

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[6]See Isakson I, col. 31, line 46-51; Isakson II, page 46, line 27-33.

[7]See Paper 7 at page 4.

[8] See Isakson I, col. 1, lines 21-55; Isakson II, page1, line 16 through page 2, line 16. Arachidonic acid may be oxygenated via either the cyclooxygenase pathway (to produce prostaglandins) or via the lipoxygenase pathway (to produce leukotrienes). 5-LO converts arachidonic acid to leukotriene A_4 (LTA4), which is then converted to LTB4 by the LTA4 hydrolase enzyme. Thus, an LTA4 inhibitor is different from a 5-LO inhibitor, in that the latter prevents the formation of LTA4 from arachidonic acid, while the former prevents the conversion of LTA4 to LTB4.

[9]See Paper 7 at page 4.

[10]Br. J. Rheumatol. (1996) 35:4-12.

inhibitors, leukocyte inhibitors and 5-LO inhibitors, as suggested by the Office and required by claim 9.

A claim is anticipated only if each and every element as set forth in the claim is described in a single prior art reference.[11] None of Isakson I or II, Gregory et al., or Engelhardt disclose combinations or pharmaceutical compositions of a COX-2 inhibitor, a 5-LO inhibitor and an immunosuppressive drug, as required by claim 9. Because none of these references disclose every element of claim 9, these references do not anticipate claim 9. Moreover, claims 10-20, which depend from claim 9, are likewise patentable over these references for the reasons stated with respect to claim 9.

Additionally, in its rejection, the Office asserts that the instant application is to be examined under 35 U.S.C.§ 102(e) as it existed prior to the amendment by the American Inventors Protection Act of 1999, because the application was not filed on or after November 29, 2000 or voluntarily published under § 122(b). Applicants respectfully note that this statement is incorrect: the instant application was filed on March 15, 2002. Thus, § 102(e) as amended by the AIPA should be applied.

IV. Rejection of claims 9-20 under 35 U.S.C. § 103(a)

Reconsideration is requested of the rejection of claims 9-20 under § 103(a) as obvious in view of Isakson I, Gregory et al., Isakson II, and Engelhardt.

Claims are *prima facie* obvious in view of particular references if the office can demonstrate that (1) the references, alone or together, describe every element of the claims, (2) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references, and (3) there is some reasonable expectation of success.[12] In this case, the Office has not met this legal standard.

As detailed above, Isakson I and Isakson II describe compositions comprising a COX-2 inhibitor and a 5-LO inhibitor. Both also mention that the pharmaceutical compositions may further comprise a pharmaceutically-acceptable carrier, diluent and/or adjuvant, "and, if desired, other active ingredients."[13] But the bare assertion found in Isakson I and II that the pharmaceutical compositions they describe may

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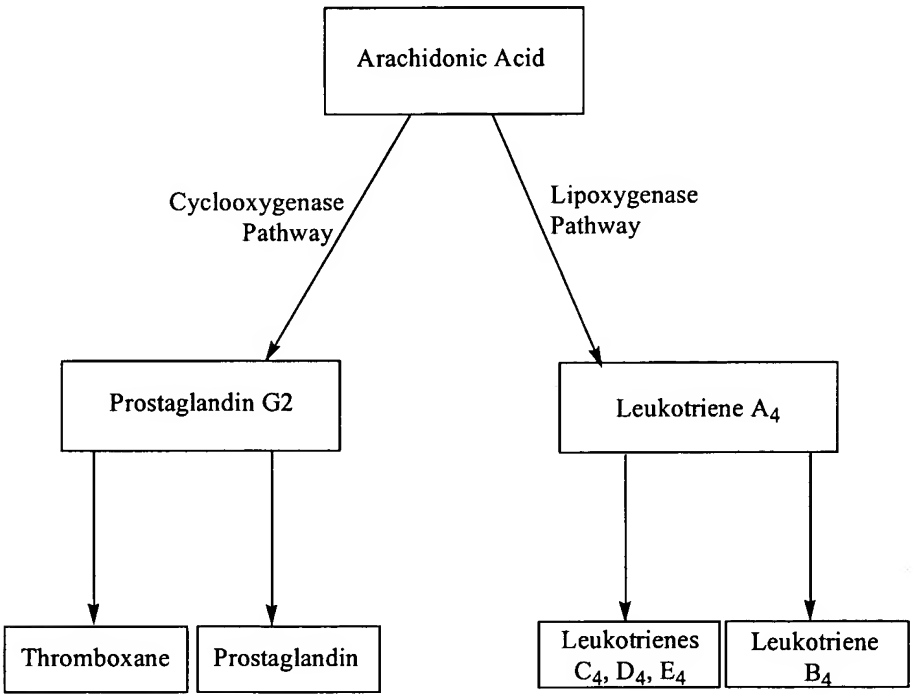
[11]Verdegaal Bros. v. Union Oil Co. of Calif., 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987). See MPEP §2131.

[12]See MPEP § 2142.

[13]See Isakson I, col. 31, line 46-51; Isakson II, page 46, line 27-33.

further comprise, if desired, other active ingredients, would not have motivated one skilled in the art to select the particular immunosuppressive agents required by claim 9. Isakson I and II also provide no instruction as to which other active ingredients may successfully be combined with the compositions they describe. Moreover, considering the two separate biochemical pathways associated with the breakdown of arachidonic acid, it would not have been obvious to the skilled artisan to simply add an immunosuppressive agent to the composition disclosed by Isakson I and II (i.e. a COX-2 inhibitor and a 5-LO inhibitor) to arrive at the composition of claim 9. As detailed in the diagram below,[14] arachidonic acid may be oxygenated via either the cyclooxygenase pathway to produce prostaglandins or via the lipoxygenase pathway to produce leukotrienes.



Prostagladin G2 and leukotriene A4 are then converted into numerous other products, such as thromboxane, prostaglandins, or any of leukotrienes B4, C4, D4, or E4, which are direct mediators of numerous inflammatory responses. The composition disclosed in Isakson I and II effectively inhibits the breakdown of arachidonic acid via either the COX-2 mediated pathway or the 5-LO mediated pathway before any compounds that elicit an immune response are produced. Therefore, the skilled artisan

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[14]See, for example, Kuby, Janis, Immunology, 3rd edition (W.H. Freeman and Company, 1997) at page 368. A copy of this page is enclosed.

empowered with the disclosure of Iskakson I and II along with the knowledge of arachidonic acid metabolism, would not have added an immunosuppressant to the composition disclosed in Isakson because the composition effectively prevents any immune response resulting from arachidonic acid metabolism, thereby seemingly making the need for an immunosuppressant unnecessary.

The deficiencies of Isakson I and II cannot be overcome by resort to Gregory et al. Gregory et al., as detailed in section III, disclose compositions comprising a COX-2 inhibitor, **a leukotriene A_4 hydrolase** (LTA4) inhibitor, and an immunosuppressive agent. The composition of claim 9, on-the-other-hand, comprises a COX-2 inhibitor, a **5-LO inhibitor** and an immunosuppressive agent. Nowhere do Gregory et al. disclose or suggest the benefit of either adding an immunosuppressive agent to the composition disclosed in Isakson I and II (i.e. a COX-2 inhibitor and 5-LO inhibitor) or the benefit of adding a 5-LO inhibitor to their composition.

In fact, the collective disclosure of Gregory et al. and Isakson I and II, actually teaches away from adding an immunosuppressive agent to the composition of claim 9. Referring to the diagram detailing arachidonic acid metabolism, the composition of Gregory et al. inhibits the COX mediated pathway before any mediator of an inflammatory response is produced. But a LTA4 inhibitor only prevents the conversion of LTA4 to the proinflammatory agent, LTB4.[15] It does not prevent the conversion of LTA4 into the proinflammatory agents LTC4, LTD4 and LTE4. Gregory et al. include an immunosuppressive agent in their composition to diminish the immune response elicited by the proinflammatory factors LTC4, LTD4, and LTE4. The composition of Isakson I and II, contrastingly, prevents any immune response resulting from arachidonic acid metabolism and they do not include an immunosuppressant in their composition. Taken together, the cited art teaches away from adding an immunosuppressant to a composition comprising a COX-2 inhibitor and a 5-LO inhibitor, as required by claim 9.

Moreover, the deficiencies of Isakson I, II, and Gregory et al. cannot be overcome by resort to Engelhardt. Engelhardt discloses that a new non-steroidal anti-inflammatory drug (NSAID), meloxicam, is able to inhibits COX-2 leukocyte migration. While this may be important for understanding the biochemical mechanism of meloxicam, it does not render claim 9 obvious. Nowhere does Engelhardt disclose or suggest a composition comprising a COX-2 inhibitor, a 5-LO inhibitor and an

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[15]See Isakson I, col. 1, lines 21-55; Isakson II, page1, line 16 through page 2, line 16.

immunosuppressant, as required by claim 9.

Unable to establish a *prima facie* case of obviousness, it appears that the Office has effectively slipped into an improper "obvious to try" analysis, informed by hindsight which Applicants' disclosure affords. But the courts have consistently held that the test for a *prima facie* case of obviousness is not whether an invention is obvious to try.[16] Instead, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references, and there must be some reasonable expectation of success. Again, the Office has not met this legal standard. Even assuming, *arguendo,* each reference cited by the Office discloses exactly what the Office says it does[17], the Office has provided no reason or rationale as to why a skilled artisan would be motivated to combine the disclosure of Gregory et al. with that of Isakson I or II or Engelhardt. For example, why would it have been obvious to modify the composition disclosed in Isakson I or II so as to include an immunosuppressive drug as allegedly disclosed by Engelhardt? Instead, the Office asserts in 8 lines of bare assertions what each reference purportedly discloses and then concludes that claims 9-20 are obvious. To properly establish a *prima facie* case of obviousness, as noted above, the law requires more than conclusions supported by bare assertions.

For the foregoing reasons, the Office has failed to establish that claim 9 is *prima facie* obvious in view of Isakson I, Gregory et al., Isakson II and Englehardt. Moreover, claims 10-20, which depend from claim 9, are likewise patentable over these references for the reasons stated with respect to claim 9.

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[16] See In re O'Farrell, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988).

[17]See section III regarding Applicant's position on the correctness of the Office's interpretation of what the cited art discloses.

VERSION WITH MARKINGS SHOWING CHANGES MADE

IN THE SPECIFICATION:

At page nine, immediately after the paragraph ending on line 4, a paragraph and table were added.

The paragraph beginning at page 11, line 35, has been amended as follows:

Compositions of the invention would also be useful in adjunct therapy involving, typically, coadministration with an additional immunosuppressive agent, such as a cyclosporin compound, or Fujisawa FK-506 **[(macrolide lactone) compond]**, or rapamycin, or a glucocorticoid, or an antiproliferative agent, or a monoclonal antibody such as an anti-CD3 (anti-T cell receptor antibody) or anti-CD5/CD7 or anti-CD4 agent, or an anti-IL-2 receptor (anti-cytokine receptor antibody) agent or an anti-IL-2 (anti-cytokine antibody), or Nippon NKT-01 (15-deoxyspergualin) or Syntex RS-61443.

The paragraph beginning at page 13, line 1, has been amended as follows:

Preferred 5-lipoxygenase inhibitors include masoprocol, tenidap, zileuton, flobufen, lonapalene, tagorizine, Abbott A-121798, Abbott A-76745, **[N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea (Abbott A-78773), (R)(+)N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea (Abbott A-79175),]** Abbott A-78773, Abbott A-79175, Abbott ABT 761, Dainippon AL-3264, Bayer Bay-x-1005, Biofor BF-389, bunaprolast, Cytomed CMI-392, Takeda CV-6504, **[Efamol EF-40,]** enazadrem phosphate, Leo Denmark ETH-615, flezelastine hydrochloride, Merck Frosst L 663536, Merckle ML-3000, **[3M Pharmaceuticals R-840,]** rilopirox, Schering Plough SCH 40120, tepoxalin, linazolast (TMK-688), **[Tanabe T-757, Tanabe T-799,]** Zeneca ZD-2138, **[Abbott A 72694, Abbott A-80263, Biofor BF-397,]** Briston-Meyers Squibb BU-4601A, carbazoycin C, lagunamycin, Wellcome BW-70C, Ciba-Geigy CGS-26529, Warner-Lambert CI 1004, Warner-Lambert PD-136005, Warner-Lambert PD-145246, **[Elsai]** Eisai E 3040, Fujirebio F-1322, **[Fisons FPL-64170,]** Fujisawa FR 110302, **[Nippon Hypox HX 0386,]** Merck & Co L-699333, Merck Frosst L 739010, Lilly LY-269415, Lilly LY 178002, **[Meiji Milk MM-7002, Hoechst Roussel P 8892, Hoechst Roussel P 8977,]** SmithKline Beecham SB-

202235, **[Green Cross SS-81-OH, Terumo Keio University TMK 685,]** American Home Products WAY-121520, **[American Home Products WAY-125007, Z n ca ZD 7717,]** Zeneca ZM-216800, Zeneca ZM 230487, 1,2-dihydro-n-(2-thiazolyl)-1-oxopyrrolo(3,2,1-kl)phenothiazine-1-carboxamide, Abbott A-65260, Abbott A-69412, **[Abbott]** Abbott-63162, American Home Products AHR-5333, **[Bayer Bay-q-1531,]** Boehringer Ingelheim BI-L-357, Boehringer Ingelheim BI-L-93BS, Boehringer Ingelheim BIL 226XX, **[Briston]** **Bristol**-Myers Squibb BMY-30094, carbazomycin B, **[Wellcome BW 4C,]** Wellcome BW-B218C, **[Wellcome BW-B70C,]** Chauvin CBS-1114, Ciba-Geigy CGS-21595, Ciba Geigy CGS-22745, Ciba-Geigy CGS-23885, Ciba-Geigy CGS-24891, Ciba-Geigy CGS-8515, Chiese CHF-1909, Warner-Lambert CI-986, Warner-Lambert CI-987, cirsiliol, docebenone, DuPont Merck **[CuP]** **DuP**-654, Eisai E 5110, Eisai E-6080, **[Green Cross EN-105,]** enofelast, epocarbazolin-A, eprovafen, evandamine, forsythiaside, Fisons FPL 62064, **[Glaxo GR-80907,]** Zeneca ICI-211965, **[isoflavans,]** Kyowa Hakko KF-8940, Merck & Co L-651392, Merck & Co L-651896, Merck & Co L-652343, Merck & Co L-656224, Merck & Co L-670630, Merck & Co L-674636, **[Merck & Co L-691816,]** Lilly LY-233569, **[Lilly LY-280810,]** Merck & Co MK-591, Merck & Co MK-886, nitrosoxacin-A, Ono ONO-5349, Ono ONO-LP-219, Ono ONO-LP-269, Warner-Lambert PD-127443, Purdue Frederick PF-5901, Sandoz QA-208-199, **[Johnson & Johnson R-68151, Johnson & Johnson R-85355,]** Rhone-Poulenc Rorer Rev-5367, Rhone-Poulenc Rorer RG-5901-A, Rhone-Poulenc Rorer RG-6966, **[Roussel-Uclaf RU-4607,]** Searle SC-41661A, Searle SC-45662, **[Sandoz SDZ-210-610,]** SmithKline Beecham SK&F-104351, SmithKline Beecham SK&F-104493, SmithKline Beecham SK&F-105809, **[Synthelabo SL-81-0433,]** Teijin TEI-8005, Terumo TMK-777, Terumo TMK-781, Terumo TMK-789, Terumo TMK-919, Terumo TMK-992, **[Teikoku Hormone TZI-2721,]** Teikoku Hormone TZI-41127, American Home Products WAY-120739, American Home Products WY 47288, American Home Products WY-48252, American Home Products Wy-50295, and Yoshitomi Y-19432.

The paragraph beginning at page 14, line 23, has been amended as follows:

More preferred 5-lipoxygenase inhibitors include masoprocol, tenidap, zileuton, flobufen, lonapalene, tagorizine, Abbott A-121798, Abbott A-76745, **[N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea (Abbott A-78773), (R)(+)N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea (Abbott A-79175),]** **Abbott A-78773, Abbott A-79175,** Abbott ABT 761, Dainippon AL-

3264, Bayer Bay-x-1005, Biofor BF-389, bunaprolast, Cytomed CMI-392, Takeda CV-6504, **[Efamol EF-40,]** Ciba-Geigy CGS 26529, enazadrem phosphate, Leo Denmark ETH-615, flezelastine hydrochloride, **[Ionapalene,]** Merck Frosst L 663536, Merck Frosst L 699333, Merckle ML-3000, **[3M Pharmaceuticals R-840,]** rilopriox, Schering Plough SCH 40120, tepoxalin, linazolast (TMK-688), **[Tanabe T-757, Tanabe T-799,]** Zeneca ZD 7717, Zeneca ZM-216800, Zeneca ZM 230487, and Zeneca ZD-2138.

The paragraph beginning at page 15, line 1, has been amended as follows:

Even more preferred 5-lipoxygenase inhibitors include tenidap, zileuton, flobufen, Ionapalene, tagorizine, Abbott A-121798, Abbott A-76745, **[N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea (Abbott A-78773), (R)(+)N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea (Abbott A-79175),]** **Abbott A-78773, Abbott A-79175,** Abbott ABT 761, Ciba-Geigy CGS 26529, Biofor BF-389, Cytomed CMI-392, Leo Denmark ETH-615, **[Ionapalene,]** Merck Frosst L 699333, Merckle ML-3000, **[3M Pharmaceuticals R-840,]** linazolast (TMK-688), **[Tanabe T-757, Tanabe T-799,]** Zeneca ZD 7717, Zeneca ZM-216800, Zeneca ZM 230487, and Zeneca ZD-2138.

IN THE CLAIMS:

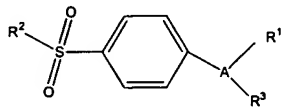
CLAIM 9:

9. (once amended) A **[**combination**]** **composition** comprising a therapeutically-effective amount of a cyclooxygenase-2 inhibition, a 5-lipoxygenase inhibitor and an immunosuppressive drug selected from antiproliferation agents, antiinflammatory-acting compounds and inhibitors of leukocyte activation.

CLAIM 10:

10. (once amended) The **[**combination**]** **composition** of Claim 9 wherein the cyclooxygenase-2 inhibitor is selected from **[**Dupont Dup-697**]** **5-bromo-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-thiophene**, **[**Taisho NS-398**]** **N-[2-cyclohexyloxy)-4-nitrophenyl]-methanesulfonamide**, **[**meloxicam**]** **1,1-dioxide-4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamid** ,

[flosulide] **N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]-methanesulfonamide** and compounds of Formula I



wherein A is a 5-or 6-member ring substituent selected from partially unsaturated or unsaturated heterocyclo and carbocyclic rings;

wherein R^1 is at least one substituent selected from heterocyclo, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

wherein R^2 is selected from alkyl, and amino; and

wherein R^3 is a radical selected from halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclooxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclo, cycloalkenyl, aralkyl, heterocycloalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N–arylaminosulfonyl, arylsulfonyl, N-alkyl-N-
arylaminosulfonyl;

or a pharmaceutically-acceptable salt thereof.

CLAIM 11:

11. (once amended) The [combination] **composition** of Claim 9 wherein the 5-lipoxygenase inhibitor is selected from [masoprocol] **(R*,S*)-4,4-(2,3-dimethyl-1,4-butanediyl)bis-1,2-benzenediol**, [tenidap] **(Z)-5-Chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1H-indole-1-carboxamide**, [zileuton] **N-(1-Benz [b]thien-2-yl-ethyl)-N-hydroxyurea**, [flobufen] **4-[2',4'-difluorbiphenyl]-4-oxo-methyl-butanic**

acid, [Ionapalene] 6-chloro-2,3-dimethoxynaphthalene-1,4-diol-diacetate, [tagorizine] (2E)-N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(6-methyl-3-pyridinyl)-2-propenamide, [Abbott A-121798] 1-methyl-6-[[[3-(tetrahydr -4-methoxy-2-methyl-2H-pyran-4-yl)-2-propenyl]oxy]methyl]-2(1H)-quinolinone, [Abbott A-76745] N-Hydroxy-N-[4-[3-(4-fluorophenoxy)phenyl]-3-butyn-2-yl]-urea, [N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea (Abbott A-79175)] N-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea, [(R)(+)N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea (Abbott A-79175)] N-[3-[5-(4-fluorophenoxy)-2-furanyl]-1-methyl-2-propynyl]-N-hydroxyurea, [Abbott ABT 761] (R)-(+)-N-[3-[5-[(4-fluorophenyl)methyl]-2-thienyl]-1-methyl-2-propynyl]-N-hydroxyurea, [Dainippon AL-3264] N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(6-methyl-3-pyridyl) acrylamide, [Bayer Bay-x-1005] (R)-2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cyclopentyl-acetic acid, [Biofor BF-389] dihydro-4-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-methyl-2H-1,2-oxazin-3(4H)-one, [bunaprolast] 2-butyl-4-methoxy-1-naphthalenol-acetate, [Cytomed CMI-392] N'-[[2-[2-[(4-chlorophenyl)thio] ethoxy]-3-methoxy-5-[(2R,5R)-tetrahydro-5-(3,4,5-trimethoxyphenyl)-2-furanyl] phenyl]methyl]-N-hydroxy-N-methyl-urea, [Takeda CV-6504] 2,3,5-Trimethyl-6-(3-pyridylmethyl)-1,4-benzoquinone, [Efamol EF-40, enazadrem phosphate] 4,6-dimethyl-2-[(6-phenyl hexyl)amino]-5-pyrimidinol phosphate (1:1) (salt), [Leo Denmark ETH-615] 4-(2-quinolylmethoxy)-N-(3-fluorobenzyl-phenyl-amino-methyl-4-benzoic-acid, [flexelastine hydrochloride] 4-[(4-fluorophenyl) methyl]-2-[hexahydro-1-(2-phenylethyl)-1H-azepin-4-yl]-1(2H)-phthalazinone, [Merck Frosst L 663536] 3-[1-(4-chlorobenzyl)-3-*t*-butyl-thio-5-isopropylindol-2-yl]-2, 2-dimethylpropanoic acid, [Merckle ML-3000] [2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2, 3-dihydro-1H-pyrrolizine-5-yl]-acetic acid, [3M Pharmaceuticals R-840, rilopirox] 6-[[4-(4-chlorophenoxy) phenoxy]methyl]-1-hydroxy-4-methyl-2(1H)-pyridinone, [Schering Plough SCH 40120] 10-(3-chlorophenyl)-6,8,9,10-tetrahydro-benzo[b][1,8]naphthyridin-5(7H)-one, [tepoxalin] 5-(4-chlorophenyl)-N-hydroxy-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-propanamide, [linazolast (TMK-688)] 1-([5-(3-methoxy-4-ethoxycarbonyloxyphenyl)-2,4-pentadienoyl]aminoethyl)-4-diphenylmethoxypiperidine, [Tanabe T-757, Tanabe T-799, Zeneca ZD-2138] 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone, [Abbott A 72694, Abbott A-80263, Biofor BF-397, Bristol-Myers Squibb BU-4601A] 2-amino-5-hydroxy-8-methylnonyl ester-benzoic acid, [carbazoycin C] 3,6-dimethoxy-1,2-dimethyl-9H-carbazol-4-ol, [lagunamycin] 6-diazo-3-methyl-4-[(1E)-

1,3,5-trimethyl-1-hexenyl]-2,5,7,8(1H,6H)-quinolinetetrone, [Wellcome BW-70C, Ciba-Geigy 26529] N-[2-[[2-[(4'-fluoro[1,1'-biphenyl]-4-yl)methyl]-1,2,3,4-tetrahydro-1-oxo-6-isoquinolinyl]oxy]ethyl]-N-hydroxy-urea, [Warner-Lambert CI 1004] (Z)-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methylene]-2-imino-4-thiazolidinone-methanesulfonate salt, [Warner-Lambert PD-136005, Warner-Lambert PD-145246] 4-[4,6-bis-t-butyl-5-hydroxy-2-pyrimidinyl]-1,3-dihydro-5-methyl-2H-imidazol-2-one, [Elsai E 3040] 6-hydroxy-5,7-dimethyl-2-methylamino-4-(3-pyridylmethyl)-benzothiazole, [Fujirebio F-1322] N-[2-(4-(benzhydryloxy)piperidino)ethyl]-3-hydroxy-5-(3-pyridylmethoxy)-2-naphthamide, [Fisons FPL-64170, Fujisawa FR 110302] 2,2-dibutyl-1,2,3,4-tetrahydro-5-(2-quinolinylmethoxy)-1-naphthalenol, [Nippon Hypox HX 0386, Merck & Co L-699333] (2-[2-[1-(4-chlorobenzyl)-4-methyl-6-[(5-phenylpyridin-2-yl)methoxy]-4,5-dihydro-1H-thiopyrano[2,3,4-cd]indol-2-yl]ethoxy]-butanoic acid, [Merck Frosst L 739010] 1,6-anhydro-3-C-[6-[[[7-cyano-5-(3-furanyl)-2-naphthal enyl]oxy]methyl]-2-pyridinyl]-2,4-dideoxy-*b*-D-threo-hexopyranose, [Lilly LY-269415] 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxy phenyl]methylene]-3-(methylamino)-4-thiazolidinone, [Lilly LY 178002] 5-[[3,5-bis(1,1-dimethyl ethyl)-4-hydroxyphenyl]methylene]-4-thiazolidinone, [Meiji Milk MM-7002, Hoechst Roussel P 8892, Hoechst Roussel P 8977, SmithKline Beecham SB-202235] (S)-N-hydroxy-N-(2,3-dihydro-6-phenylmethoxy-3-benzyofuranyl)-urea, [Green Cross SS-81-OH, Terumo Keio University TMK 685, American Home Products WAY-121520] 1-[(4-chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid, [American Home Products WAY-125007, Zeneca ZD 7717, Zeneca ZM-216800] 2-[2,3-dihydro-1-methoxy-6-(2-naphthalenylmethoxy)-1H-inden-1-yl]-thiazole, [Zeneca ZM 230487] (6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxymethyl]-1-ethyl-2-quinolone, 1,2-dihydro-n-(2-thiazolyl)-1-oxopyrrolo(3,2,1-kl)phenothiazine-1-carboxamide, [Abbott A-65260] tetrahydro-1-phenyl-1,2,4-triazin-3(2H)-one, [Abbott A-69412] N-[1-(3-Furyl)ethyl]-N-hydroxyurea, [Abbott Abbott-63162] N-hydroxy-N-[1-[4-(phenylmethoxy)phenyl]ethyl]-acetamide, [American Home Products AHR-5333] 1-[4-[3-[4-[bis(4-fluorophenyl)hydroxymethyl]-1-piperidinyl]propoxy]-3-methoxyphenyl]-ethanone, [Bayer Bay-q-1531, Boehringer Ingelheim BI-L-357] mono[2,6-dimethyl-4-[(1E)-2-(2-thienyl) ethenyl]phenyl]-butanedioic acid, [Boehringer Ingelheim BI-L-93BS] 2,6-bis(1,1-dimethylethyl)-4-[2-(3-pyridinyl)ethenyl]-phenol, [Boehringer Ingelheim BIL 226XX] 2,6-dimethyl-4-[2-(2-thienyl)ethenyl]-phenol, [Bristol-Myers Squibb BMY-30094] 9-phenylnonanophydroxamic acid, [carbazomycin B] 4-hydroxy-3-methoxy-1,2-

dimethylcarbazole, [Wellcome BW 4C, Wellcome BW-B218C] N-hydroxy-N-[1-methyl-3-(3-phenoxyphenyl)-2-propenyl]-acetamide, [Wellcome BW-B70C, Chauvin CBS-1114] 2-phenylhydrazide-benzenecarboximidic acid, [Ciba-Geigy CGS-21595] 4-(cyclohexyl methylamino)-1,2-naphthalenediol, diacetate ester, [Ciba-Geigy CGS-22745] (2E)-3-[4-(2,5-dimethyl-1H-pyrrol-1-yl)phenyl]-N-hydroxy-N-methyl-2-propenamide, [Ciba-Geigy CGS-23885] N-hydroxy-N-[(6-phenoxy-2H-1-benzopyran-3-yl)methyl]-urea, [Ciba-Geigy CGS 24891] N-[[6-(4-fluorophenoxy)-2H-1-benzopyran-3-yl]methyl]-N-hydroxy-N-methyl-urea, [Ciba-Geigy CGS-8515] methyl 2-[(3,4-dihydro-3,4-dioxo-1-naphthalenyl)amino]-benzoate, [Chiesi CHF-1909] monohydrobromide-6-(2,2-dimethylhydrazino)-5,6,7,8-tetrahydro-1,2-naphthalenediol, [Warner-Lambert CI-986] 5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazole-2(3H)-thione, choline salt, [Warner-Lambert CI 987] 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione, [cirsiliol] 3',4',5-trihydroxy-6,7-dimethoxyflavone, [docebenone] 3,5,6-trimethyl--1,4-dione- 2-(12-hydroxy-5,10-dodecadiynyl)-2,5-cyclohexadiene, [DuPont Merck DuP-654] 2-benzyl-1-naphthol, [Eisai E 5110] N-methoxy-3-(3,5-di-tert-butyl-4-hydroxybenzylidene pyrrolidin-2-one, [Eisai E-6080] 6-hydroxy-2-(4-sulfamoylbenzylamino)-4,5,7-trimethylbenzothiazole hydrochloride, [Green Cross EN-105, enofelast] 4-[(1E)-2-(4-fluorophenyl)ethenyl]-2,6-dimethyl-phenol, [epocarbazolin-A] 1,6-diol, 4-(hydroxymethyl)-7-methyl-8-[3-methyl-3-(3-methylbutyl) oxiranyl]-9H-carbazole, [eprovafen] 5-(3-phenylpropyl)-2-thiophenepentanoic acid, [evandamine] 4,5-dihydro-5-methyl-1-(4,5,6,7-tetrahydro-2-benzothiazolyl)-1H-pyrazol-3-amine, [forsythiaside] 4-[(2E)-3-(3,4-dihydroxyphenyl)-2-propenoate]-2-(3,4-dihydroxy phenyl)ethyl-6-O-(6-deoxy-a-L-mannopyranosyl)-*b*-D-Glucopyranoside, [Fisons FPL 62064] N-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-amine, [Glaxo GR-80907, Zeneca ICI-211965] 1-[3-(naphth-2-ylmethoxy)phenyl]-1-(thiazol-2-yl)propyl methyl ether, [isoflavans, Kyowa Hakko KF-8940] 2-N-heptyl-4-hydroxyquinoline-N-oxide, [Merck & Co L-651392] 4-bromo-2,7-dimethoxy-3,4-phenothizin-3-one, [Merck & Co L-651896] 6-[1-[2-(hydroxymethyl)phenyl]-1-propen-3-yl]-2,3-dihydro-5-benzofuranol, [Merck & Co L-652343] 3-hydroxy-5-trifluoromethyl-N-(2-(2-thienyl)-2-phenyl-ethenyl)-benzo(b)thiophene-2-carboxamide, [Merck & Co L-656224] 2-[(4-methoxyphenyl)methyl]-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran, [Merck & Co L-670630] 2,3-dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)-5-benzofuranol, [Merck & Co L-674636] [[4-(4-chlorophenyl)-1-[4-(2-quinolinylmethoxy)phenyl]butyl] thio]-acetic acid, [Merck & Co L-691816, Lilly LY-

233569] N-hydroxy-N-methyl-3-[2-(methylthio)phenyl]-2-propenamid , [Lilly LY-280810, Merck & Co MK-591] 3-(1((4-chlorophenyl)methyl)-3((1,1-dim thyl-ethyl)thio)-5(quinolin-2-yl-methyl-oxy)-1H-indol-2-yl)-2,2-dimethyl-propanoat , [Merck & Co MK-886, nitrosoxacin-A] N-hydroxy-14-methyl-N-nitroso-1-pentadecanamine, [Ono ONO-5349] 2-amino-4-[(4-methylphenyl)thio]- phenol hydrochloride, [Ono ONO-LP-219] (2E,11Z,14Z)-N-[2,3-dihydro-3-(1H-tetrazol-5-yl)-1,4-benzodioxin-5-yl]-N-methyl-2,11,14-eicosatrienamide, [Ono ONO-LP-269] (2E,11Z,14Z)-N-[4-hydroxy-2-(1H-tetrazol-5-yl)-8-quinolinyl]-2,11,14-eicosatrienamide, [Warner-Lambert PD-127443] (E)-2,6-bis(1,1-dimethyl-ethyl)-4-[2-(5-methyl-1H-pyrazol-3-yl)ethenyl]-phenol, [Purdue Frederick PF-5901] 2-[3(1-hydroxyhexyl)phenoxymethyl]-quinoline hydrochloride, [Sandoz QA-208-199] N-hydroxy-N-methyl-7-propoxy-2-naphthaleneethanamine, [Johnson & Johnson R-68151, Johnson & Johnson R-85355, Rhone-Poulenc Rorer Rev-5367] methyl-2-[[3-(1-hydroxypentyl) phenoxy]methyl]-benzoic acid (ester), [Rhone-Poulenc Rorer RG-5901A] a-pentyl-3-(2-quinolinylmethoxy)-benzenemethanol, [Rhone-Poulenc Rorer RG-6866] N--hydroxy-N-methyl-4-(phenylmethoxy)-benzeneacetamide, [Roussel-Uclaf RU-46057, Searl SC-41661A] 3-(3,5-bis(1,1-dimethyl)-4-hydroxyphenyl)thiol]-N-methyl-N-[2-(2-pyridinyl-propanamide), [Searle SC-45662] (R*, S*)-1-methylpropoxy]-[(1R,2S)-2-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]thio]-acetic acid, [Sandoz SDZ-210-610, SmithKline Beecham SK&F-104351] 2-(4-fluorophenyl)-6,7-dihydro-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]-imidazole, [SmithKline Beecham SK&F-104493] 6,7-dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]-imidazole, [SmithKline Beecham SK&F-105809] 2-(4-methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]-imidazole, [Synthelabo SL-81-0433, Teijin TEI-8005] (7E)-8-(2-naphthyl)-5,6-trans-5,6-methano-7-octenoic acid, [Terumo TMK-777] (2E,4E)-N-[2-[4-(diphenyl methoxy)-1-piperidinyl] ethyl]-5-(4-hydroxy-3-methoxyphenyl)-2,4-pentadienamide, [Terumo TMK-781] (2E)-N-[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]-3-(4-hydroxy-3-methoxy phenyl)-2-propenamide, [Terumo TMK-789] (2E)-N-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-3-(4-hydroxy-3-methoxy phenyl)-2-propenamide, [Terumo TMK-919] (2Z,5Z,8Z,11Z,14Z,17Z)-N-[4-[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propenyl]amino]butyl]-2,5,8,11,14,17-eicosahexaenamide, [Terumo TMK-992] (2E)-N-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl]ethyl]-3-(4-hydroxy-3-methoxyphenyl)-2-propenamide, [Teikoku Hormone TZI-2721, Teikoku Hormone TZI-41127] 2-(4-hydroxy-3,5-dimethylphenyl)-5-methoxy-3-methylindole, [American Home Products

WAY-120739] 1,8-diethyl-1,3,4,9-tetrahydro-6-(2-quinolinylmethoxy)-pyrano[3,4-b]indole-1-acetic acid, [American Home Products WY 47288] 2-[(1-naphthalenyloxy)methyl]-quinoline, [American Home Products Wy-48252] 1,1,1-trifluoro-N-[3-(2-quinolinylmethoxy)phenyl]-methanesulfonamide, [American Home Products Wy-50295] α-methyl-6-(2-quinolinylmethoxy)-2-naphthalene-acetic acid, and [Yoshitomi Y-19432] 1-butyl-5-hydroxy-2-methyl-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-indole-3-carboxamide, hydrochloride.

CLAIM 12:

12. (once amended) The [combination] **composition** of Claim 11 wherein the 5-lipoxygenase inhibitor is selected from [masoprocol] (R*,S*)-4,4-(2,3-dimethyl-1,4-butanediyl)bis-1,2-benzenediol, [tenidap] (Z)-5-Chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1H-indole-1-carboxamide, [zileuton] N-(1-Benzo[b]thien-2-yl-ethyl)-N-hydroxyurea, [flobufen] 4-[2',4'-difluorbiphenyl]-4-oxo-methyl-butanic acid, [lonapalene] 6-chloro-2,3-dimethoxynaphthalene-1,4-diol-diacetate, [tagorizine] (2E)-N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(6-methyl-3-pyridinyl)-2-propenamide, [Abbott A-121798] 1-methyl-6-[[[3-(tetrahydro-4-methoxy-2-methyl-2H-pyran-4-yl)-2-propenyl]oxy]methyl]-2(1H)-quinolinone, [Abbott A-76745] N-Hydroxy-N-[4-[3-(4-fluorophenoxy)phenyl]-3-butyn-2-yl]-urea, [N'-[[5-4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N'-hydroxyurea (Abbott A-78773)] N-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea, [(R)(+)N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea (Abbott A-79175)] N-[3-[5-(4-fluorophenoxy)-2-furanyl]-1-methyl-2-propynyl]-N-hydroxyurea, [Abbott ABT 761] (R)-(+)-N-[3-[5-[(4-fluorophenyl)methyl]-2-thienyl]-1-methyl-2-propynyl]-N-hydroxyurea, [Dainippon AL-3264] N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(6-methyl-3-pyridyl) acrylamide, [Bayer Bay-x-1005] (R)-2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cyclopentyl-acetic acid, [Biofor BF-389] dihydro-4-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-methyl-2H-1,2-oxazin-3(4H)-one, [bunaprolast] 2-butyl-4-methoxy-1-naphthalenol-acetate, [Cytomed CMI-392] N'-[[2-[2-[(4-chlorophenyl)thio] ethoxy]-3-methoxy-5-[(2R,5R)-tetrahydro-5-(3,4,5-trimethoxyphenyl)-2-furanyl] phenyl]methyl]-N-hydroxy-N-methyl-urea, [Takeda CV-6504] 2,3,5-Trimethyl-6-(3-pyridylmethyl)-1,4-benzoquinone, [Efamol EF-40 , Ciba-Geigy CGS-26529] N-[2-[[2-[(4'-fluoro[1,1'-biphenyl]-4-yl)methyl]-1,2,3,4-tetrahydro-1-oxo-6-isoquinolinyl]oxy]ethyl]-N-hydroxy-urea, [enazadrem phosphate] 4,6-dimethyl-2-[(6-phenyl hexyl)amino]-5-

pyrimidinol phosphate (1:1) (salt), [Leo Denmark ETH-615] 4-(2-quinolylm thoxy)-N-(3-fluorobenzyl-phenyl-amino-methyl-4-benzoic-acid, [flexelastine hydrochloride] 4-[(4-fluorophenyl) methyl]-2-[hexahydro-1-(2-phenylethyl)-1H-azepin-4-yl]-1(2H)-phthalazinone, [lonapalene] 6-chloro-2,3-dimethoxynaphthalene-1,4-diol-diacetate, [Merck Frosst L 663536] 3-[1-(4-chlorobenzyl)-3-*t*-butyl-thio-5-isopropylindol-2-yl]-2, 2-dimethylpropanoic acid, [Merck Frosst L 699333] (2-[2-[1-(4-chlorobenzyl)-4-methyl-6-[(5-phenylpyridin-2-yl)methoxy]-4,5-dihydro-1H-thiopyrano[2,3,4-cd]indol-2-yl]ethoxy]-butanoic acid, [Merckle ML-3000] [2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2, 3-dihydro-1H-pyrrolizine-5-yl]-acetic acid, [3M Pharmaceuticals R-840, rilopirox] 6-[[4-(4-chlorophenoxy) phenoxy]methyl]-1-hydroxy-4-methyl-2(1H)-pyridinone, [Schering Plough SCH 40120] 10-(3-chlorophenyl)-6,8,9,10-tetrahydro- benzo[b][1,8]naphthyridin-5(7H)-one, [tepoxalin] 5-(4-chlorophenyl)-N-hydroxy-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-propanamide, [linazolast (TMK-688)] 1-([5-(3-methoxy-4-ethoxycarbonyloxyphenyl)-2,4-pentadienoyl]aminoethyl)-4-diphenylmethoxypiperidine, [Tanabe T-757 , Tanabe T-799, Zeneca ZD 7717, Zeneca ZM-216800] 2-[2,3-dihydro-1-methoxy-6-(2-naphthalenylmethoxy)-1H-inden-1-yl]-thiazole, [Zeneca ZM 230487] (6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxymethyl]-1-ethyl-2-quinolone, and [Zeneca Zd-2138] 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone.

CLAIM 13:

13. (once amended) The [combination] **composition** of Claim 12 wherein the 5-lipoxygenase inhibitor is selected from [tenidap] (Z)-5-Chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1H-indole-1-carboxamide, [zileuton] N-(1-Benzo[b]thien-2-yl-ethyl)-N-hydroxyurea, [flobufen] 4-[2',4'-difluorbiphenyl]-4-oxo-methyl-butanic acid, [lonapalene] 6-chloro-2,3-dimethoxynaphthalene-1,4-diol-diacetate, [tagorizine] (2E)-N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(6-methyl-3-pyridinyl)-2-propenamide, [Abbott A-121798] 1-methyl-6-[[[3-(tetrahydro-4-methoxy-2-methyl-2H-pyran-4-yl)-2-propenyl]oxy]methyl]-2(1H)-quinolinone, [Abbott A-76745] N-Hydroxy-N-[4-[3-(4-fluorophenoxy)phenyl]-3-butyn-2-yl]-urea, [N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-n'-hydroxyurea (Abbott A-78773)] N-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea, [(R)(+)N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea (Abbott

A-79175)] **N-[3-[5-(4-fluorophenoxy)-2-furanyl]-1-methyl-2-propynyl]-N-hydroxyurea**, [Abbott ABT 761] **(R)-(+)-N-[3-[5-[(4-fluorophenyl)methyl]-2-thienyl]-1-methyl-2-propynyl]-N-hydroxyurea**, [Ciba-Geigy CGS-26529] **N-[2-[[2-[(4'-fluoro[1,1'-biphenyl]-4-yl)methyl]-1,2,3,4-tetrahydro-1-oxo-6-isoquinolinyl]oxy]ethyl]-N-hydroxy-urea**, [Biofor BF-389] **dihydro-4-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-methyl-2H-1,2-oxazin-3(4H)-one**, [Cytomed CMI, Leo Denmark ETH-615] **4-(2-quinolylmethoxy)-N-(3-fluorobenzyl-phenyl-amino-methyl-4-benzoic-acid**, [Ionapalene] **6-chloro-2,3-dimethoxynaphthalene-1,4-diol-diacetate**, [Merck Frosst L 699333] **(2-[2-[1-(4-chlorobenzyl)-4-methyl-6-[(5-phenylpyridin-2-yl)methoxy]-4,5-dihydro-1H-thiopyrano[2,3,4-cd]indol-2-yl]ethoxy]-butanoic acid**, [Merckle ML-3000] **[2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2, 3-dihydro-1H-pyrrolizine-5-yl]-acetic acid**, [3M Pharmaceuticals R-840, linazolast (TMK-688)] **1-([5-(3-methoxy-4-ethoxycarbonyloxyphenyl)-2,4-pentadienoyl]aminoethyl)-4-diphenylmethoxypiperidine**, [Tanabe T-757, Tanabe T-799, Zeneca ZD 7717, Zeneca ZN-216800] **2-[2,3-dihydro-1-methoxy-6-(2-naphthalenylmethoxy)-1H-inden-1-yl]-thiazole**, [Zeneca ZM 230487] **(6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxymethyl]-1-ethyl-2-quinolone**, and [Zeneca ZD-2138] **6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone**.

CLAIM 14:

14. (once amended) The [combination] **composition** of claim 10 wherein A is selected from oxazolyl, isoxazolyl, thienyl, dihydrofuryl, furyl, pyrrolyl, pyrazolyl, thiazolyl, imidazolyl, isothiazolyl, cyclopentenyl, phenyl, and pyridyl; wherein R^1 is selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio; wherein R^2 is selected from lower alkyl and amino; and wherein R^3 is a radical selected from halo, lower alkyl, oxo, cyano, carboxyl, lower cycloalkyl, heteroaryloxy, lower alkyloxy, lower cycloalkyl, phenyl, lower haloalkyl, 5- or 6-membered heterocyclo, lower hydroxyalkyl, lower aralkyl, acyl, phenylcarbonyl, lower alkoxyalkyl, heteroaryloxy, alkoxycarbonyl, aminocarbonyl,

alkylaminocarbonyl, alkylamino, aminoalkyl, alkylaminoalkyl, aryloxy, and aralkoxy; or a pharmaceutically-acceptable salt thereof.

CLAIM 15:

15. (once amended) The [combination] **composition** of Claim 14 wherein A is selected from oxazolyl, isoxazolyl, dihydrofuryl, imidazolyl, and pyrazolyl; wherein R^1 is selected from 5- and 6-membered heterocyclo, and aryl selected from phenyl, biphenyl and naphthyl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio; wherein R^2 is amino; and wherein R^3 is a radical selected from oxo, cyano, carboxyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, halo, lower alkyl, lower alkyloxy, lower cycloalkyl, phenyl, lower haloalkyl, 5- or 6-membered heterocyclo, lower hydroxyalkyl, lower aralkyl, acyl, phenylcarbonyl, lower alkoxyalkyl, 5- or 6-membered heteroaryloxy, aminocarbonyl, lower alkylaminocarbonyl, lower alkylamino, lower aminoalkyl, lower alkylaminoalkyl, phenyloxy, and lower aralkoxy; or a pharmaceutically-acceptable salt thereof.

CLAIM 16:

16. (once amended) The [combination] **composition** of Claim 15 wherein A is selected from oxazolyl, isoxazolyl, imidazolyl, and pyrazolyl; wherein R^1 is phenyl optionally substituted
at a substitutable position with one or more radicals selected from methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, trifluoromethyl, cyano, carboxyl, methoxycarbonyl, hydroxyl, hydroxymethyl, trifluoromethoxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N-N-dipropylamino, –butylamino, N-methyl-N-ethylamino, nitro, methoxymethyl, methylsulfinyl, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, and methylthio; wherein R^2 is amino; and wherein R^3 is a radical selected from oxo, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, carboxypropyl, carboxymethyl, carboxyethyl, cyanomethyl, fluoro, chloro, bromo, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl,

dichloroethyl, dichloropropyl, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, cyclohexyl, phenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, pyrazinyl, hydroxylmethyl, hydroxypropyl, benzyl, formyl, phenylcarbonyl, methoxymethyl, furylmethyloxy, aminocarbonyl, N-methylaminocarbonyl, –N-dimethylaminocarbonyl, N,N-methylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, aminomethyl, N,N-dimethylaminomethyl, N-methyl-N-ethylaminomethyl, benzyloxy, and phenyloxy; or a pharmaceutically-acceptable salt thereof.

CLAIM 17:

17. (twice amended) The [combination] **composition** of Claim 16 wherein the cyclooxygenase-2 inhibitor is selected from compounds, their prodrugs and their pharmaceutically-acceptable salts, of the group consisting of

3-(3,4-difluorophenyl)-4-(4-methylsulfonylphenyl)-2-(5H)-furanone;

3-phenyl-4-(4-methylsulfonylphenyl)-2-(5H)-furanone;

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-hydroxyethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

[2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; and

4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide.

If there are any additional charges in this matter, please charge Deposit Account No. 19-1345.

Respectfully submitted,

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